~~59.~~ 60. (NEW) The method of claim 22, wherein the backbone plasmid further consists of HSV Amplicon sequences required for packaging and replication.

~~60.~~ 61. (NEW) The method of claim 22, wherein the backbone plasmid further consists of one or more sequences that allow for integration of sequences into cells after viral infection.

REMARKS

Applicants have carefully reviewed and considered the Office Action mailed on June 18, 2002, and the references cited therewith. Claims 8, 10, 11-17, 22 and 25 are amended; claims 26-60 are newly added. As a result, claims 2-8 and 10-60 are now pending in this application. No new subject matter has been added. The amendments have been made to clarify the claims in order to expedite prosecution of the present application, and not for reasons of patentability. Therefore, the amendments are not intended to limit the scope of equivalents to which any claim element may be entitled. The amendments to the claims are fully supported by the specification as originally filed.

Support for new dependent claims 26-33, 42-49 and 53-60 is found in originally filed claims 2-8 and 10. Support for new dependent claims 34-37, 38-41 and 50-52 is found in originally filed claims 12-15.

Rejection of the Claims under 35 U.S.C. §112

1. Indefiniteness

Claims 2-8 and 10-16 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the examiner has indicated that claims 11 and 16 are vague and indefinite because of the use of the transitional phrase "consisting essentially of." The Office Action further states that this rejection affects all dependent claims 2-8, 10, and 12-15. This phrase has been deleted, thereby rendering this rejection moot.

Applicant respectfully requests that this rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

2. Written Description

Claims 2-16 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. The phrase "consisting essentially of" has been deleted from the pending claims, thereby rendering this rejection moot.

Applicant respectfully requests that this rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

3. New Matter

Claims 2-8 and 10-25 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor had possession of the claimed invention. Claims 2-8 and 10-25 recite that the backbone and the shuttle plasmids lack a loxP sequence. The examiner maintains that this negative limitation cannot be found in the original disclosure. Applicant disagrees with this assessment, but in order to expedite prosecution, Applicant has deleted this phrase from the claims.

Applicant requests that the Examiner withdraw the rejection under 35 U.S.C. § 112.

§103 Rejection of the Claims

1. Aoki et al. in view of Chinnadurai et al.

Claims 4, 5, 10, 11 and 13-25 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Aoki *et al.* (Molecular Medicine, 5: 224-231 (1999)) and Chinnadurai *et al.* (Journal of Virology, 32(2): 623-628 (1979)). The present claims recite a shuttle plasmid consisting of Ad sequences from 0 to 1 and 9.2 to 16.1 map units of an Ad genome, a cloning system that includes this shuttle plasmid and an Ad backbone plasmid consisting of an Ad genome lacking map units 0 to 9.2, host cells comprising this cloning system, and a method of using the cloning system. None of the pending claims include a loxP sequence.

Applicant asserts that a *prima facie* case of obviousness of the pending claims has not been established. In order to establish a *prima facie* cases of obviousness, three factors must be met. First, the references themselves must teach or suggest all the limitations of the claims. Second, there must be a reasonable expectation of success at the time the invention was made. Third, the prior art must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference, or to combine references. Applicant respectfully asserts that all of these three requirements have not been met for the pending claims.

With all due respect, the Office Action at page 9 misquotes page 226, second column of Aoki *et al.* The Office Action indicates that Aoki *et al.* teaches that "Cre recombinase produces the full-length recombinant adenoviral vector in vitro by intermolecular recombination between the loxP sites and these two [*i.e.*, Ad 9.2-16.1 m.u. in the shuttle plasmid and 9.2-100 m.u. in the cosmid] linearized molecules." [emphasis added] The Office Action continues by stating that "Aoki *et al.* teaches direct homologous recombination between the loxP sites and the overlapping parental fragments consisting of map units 9.2 to 16.1 are critical for homologous recombination to occur to generate adenovirus." In fact, the Aoki *et al.* state that "Cre recombinase produces the full-length recombinant adenoviral vector in vitro by intermolecular recombination between the loxP sites in these two linearized molecules." [emphasis added] Thus, Aoki *et al.* teach that the recombination event takes place in the loxP sequences, and not in the Ad sequences.

It should be noted that intramolecular recombination between loxP sites is taught by Aoki (and many others) is an enzyme-mediated (*i.e.*, Cre-mediated) event that catalyzes site-specific recombination (Aoki *et al.* p. 225, 1st paragraph). Aoki *et al.* continue by stating that "[o]nly two components are required to mediate recombination: the 38-kD Cre recombinase and the 34 bp loxP site. . . . If the loxP sites are present on separate linear molecules, recombinase action results in the mutual exchange of regions distal to the sites." After Cre recombinase acts on the two molecules, the 9.2-16.1 region is excised from the shuttle plasmid and replaced by the loxP-9.2-100 mu of the adenovirus cosmid DNA. (*See* figure 1A).

This Cre-mediated reaction used by Aoki is not homologous recombination. In fact, Aoki *et al.* developed this recombinase-mediated technique to overcome the limitation of Chinnadurai *et al.* as described by Aoki *et al.* on p. 224, 2nd column, line 10, "since homologous

recombination is a rare event in mammalian cells . . . .To circumvent these problems of efficiency and contamination of wild-type adenovirus, we proposed using Cre-loxP recombination in vitro." Thus, Aoki *et al.* teach that homologous recombination is inefficient and that Cre-loxP mediated intramolecular recombination (not homologous recombination) in these two linearized molecules is essential because only recombined adenoviral DNA can give rise to adenovirus.

Page 5 of the Office Action dated December 19, 2001 concedes that Aoki *et al.* does not teach a system for generating recombinant adenovirus without the Cre-lox method. Therefore, Aoki *et al.* alone does not anticipate the present invention, which does not include loxP sequences. Page 8 of the June 18, 2002 Office Action concedes that the Chinnadurai *et al.* reference alone does not teach the present invention. Thus, the only way that the present invention can be taught is if the two references are combined.

The two references, Aoki *et al.* and Chinnadurai *et al.*, cannot be logically combined, as they both teach different recombination methods. Chinnadurai *et al.* used homologous recombination, and Aoki used a recombinase-mediated technique. As discussed above, Aoki *et al.* discuss an adenoviral vector that uses the Cre-loxP system. Specifically, Aoki *et al.* teach that map units 9.2-16.1 are not sufficient generate adenovirus. Aoki *et al.* further discounts the role of map units 9.2 to 16.1 in the shuttle plasmid, as they were not included in Figure 1A. Aoki *et al.* argued that recombination would have to occur at the loxP sites to result in adenovirus, and without this recombination step, would not "give rise to adenovirus." Therefore Aoki *et al.*, who are artisans of extraordinary skill in the art and having known of the Chinnadurai *et al.* manuscript (Aoki *et al.* cited Chinnadurai *et al.* as reference #6), taught that the transfected DNA needed to consist of a single linear strand and contain map units 0-1 and the left ITR.

The Introduction section of Aoki *et al.* discusses homologous recombination in mammalian helper cells between shuttle plasmid and an overlapping DNA of virus origin that has been rendered noninfectious. Aoki *et al.* specifically cites to Chinnadurai *et al.* regarding this homologous recombination method. Aoki *et al.* continues, however, to state "since homologous recombination is a rare event in mammalian cells. These procedures are often unpredictable, time-consuming, and difficult to control. To circumvent these problems of efficiency and

contamination of wild-type adenovirus, we proposed using Cre-loxP recombination *in vitro*." Aoki at p. 224-225. Therefore, those of skill in the art (namely, Aoki *et al.*) were aware of the teachings of Chinnadurai *et al.*, and chose to use the Cre-loxP system, and not the system of the present invention. Thus, Aoki *et al.* teach away from combining their work with Chinnadurai *et al.*

It is respectfully submitted that the Examiner appears to be employing hindsight to arrive at Applicant's invention in the absence of any suggestion in the cited art to take Applicant's approach. The Examiner is reminded that it is impermissible to use Applicant's specification as a template to arrive at the conclusion that the claimed invention is obvious. *In re Fritsch*, 23 U.S.P.Q.2d 1780, 1782 (Fed. Cir. 1992). To render an invention obvious, the combination of the cited art must teach or suggest the claimed invention and provide a reasonable expectation of success in preparing the claimed invention. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); *In re O'Farrell*, 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988).

Neither of these references alone teach the present claimed invention. Further, the art teaches away from combining these two references. Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 103 be withdrawn.

2. Aoki et al. in view of Chinnadurai et al. and Krougliak et al.

Claims 2, 3 and 6 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Aoki *et al.* and Chinnadurai *et al.*, and further in view of Krougliak *et al.* (Human Gene Therapy, 6: 1575-1586 (1995)).

Krougliak *et al.* does not remedy the deficiencies of Aoki *et al.* and Chinnadurai *et al.* There is no suggestion or motivation, either in the cited references themselves or in the knowledge generally available to an art worker, to modify the references or to combine the teachings of the references so as to arrive at the claimed invention. Pending claims 2, 3 and 6 recite a two-part cloning system: the first element being a backbone plasmid consisting of map units 9.2 to 100 of an Ad genome, and the second element being a shuttle plasmid consisting of map units 0 to 1 and 9.2 to 16.1 of an Ad genome.

Krougliak *et al.* generated cell lines that could complement E1, E4 and protein IX defective adenovirus type 5 (Ad5) mutants. The plasmid system used by Krougliak *et al.* contained adenovirus sequences from the left ITR to the right ITR (*i.e.*, the full viral backbone), except for sequences encoding E1, E4 or protein IX. The intention of the deletions by Krougliak *et al.* was to provide for more space to accommodate larger inserts placed into the E1 region of the adenovirus vector and not to otherwise modify the backbone. Both Aoki *et al.* and Krougliak *et al.* devised strategies to make recombinant adenovirus only when the intact recombinant adenovirus genome that contained map units 0-1 and the left ITR was transfected into the cell. Recombination in this region was directly refuted by Aoki *et al.* and not attempted by Krougliak *et al.*, both of whom were extraordinarily skilled in the art.

Thus, none of these references, either alone or taken in combination, teach the present claimed invention. Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 103 be withdrawn.

3. Aoki et al. in view of Chinnadurai et al., Krougliak et al. and Breakfield et al.

Claims 7 and 8 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Aoki *et al.*, Chinnadurai *et al.* and Krougliak *et al.*, and further in view of Breakfield *et al.* (U.S. 5,965,441).

Breakfield *et al.* does not remedy the shortcomings of Chinnadurai *et al.*, Aoki *et al.* and Krougliak *et al.* Breakfield *et al.* teach a hybrid vector system that incorporate elements of herpes virus and adeno-associated virus that is capable of expressing a gene product in eukaryotic cells. The Examiner admits that Breakfield *et al.* is deficient in that it does not teach an adenovirus vector. The Examiner states, however, that "one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate HSV Amplicon sequences into the backbone of Aoki *et al.* to expand the host range of gene expression to dividing cells."

Again, the Examiner appears to be using hindsight to arrive at Applicant's invention, selecting aspects from four different references to attempt to piece together Applicant's invention. Even if one with skill in the art was motivated to combine these four references, when

they are logically combined, one would have the Aoki *et al.* Ad vector containing a loxP sequence and the Breakfield *et al.* AAV/HSV hybrid sequences in the Krougliak *et al.* cell line (in a backbone containing the lefthand ITR). In contrast, the plasmids used in the present claimed cloning system do not contain loxP sequences or the lefthand ITR.

Thus, none of these references, either alone or taken in combination, teach the present claimed invention. Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 103 be withdrawn.

4. Aoki et al. in view of Chinnadurai et al. and Chartier et al.

Claim 12 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Aoki *et al.* and Chinnadurai *et al.*, and further in view of Chartier *et al.* (Journal of Virology, 70(7): 4805-4810 (1996)).

Aoki *et al.* and Chinnadurai *et al.* are discussed above. Chartier *et al.* do not remedy the deficiencies of Aoki *et al.*, and Chinnadurai *et al.* Chartier *et al.* disclose the introduction of unique PacI site into and Ad5 vector.

There is no suggestion or motivation in the cited references to combine the teachings of the references so as to arrive at the claimed invention. Claim 12 recites a shuttle plasmid having Ad sequences wherein PacI restriction endonuclease sites flank either end of the Ad sequences, but does not recite a loxP sequence. If Aoki *et al.*, Chinnadurai *et al.* and Chartier *et al.* are combined, one would have the Aoki *et al.* Ad vector containing a loxP sequence and the Chartier *et al.* PacI sites. In contrast, the present claimed invention does not contain loxP sequences.

Thus, none of these references, either alone or taken in combination, teach the present claimed invention. Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 103 be withdrawn.

Conclusion

Applicants respectfully submit that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney (612-373-6961) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 17 day of Sept 2002

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Name

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Signature